29. The DNA molecule of claim 28 which comprises a nucleotide sequence that encodes the deduced amino acid sequence set forth in SEQ. ID. NO: 18 or its complement.

30. The DNA molecule of claim 29 which comprises the nucleotide sequence set forth in SEQ. ID. NO: 18 or its complement.

31. Recombinant host cells which are modified to contain the DNA molecule of claim 28.

32. A method to produce a calcium ion channel α_1 subunit protein which method comprises culturing the cells of claim 31 under conditions wherein said expression system produces said protein.

33. A method to prepare cells which produce a calcium ion channel α_1 subunit protein which method comprises introducing into said cells the DNA molecule of claim 28.--

REMARKS

The claims have been amended to clarify the nature of the invention and to respond to some of the rejections under 35 U.S.C. § 112, second paragraph. No new matter has been added and entry of the amendment is respectfully requested.

The Invention

The invention resides in the construction of a novel nucleotide sequence and the recovery and disclosure of a human clone, each of which encodes a protein that is the α_1 subunit of a previously unknown calcium ion channel. The protein which comprises the amino acid sequence set forth in SEQ. ID. NO: 19 is seen to correspond to that encoded by positions 701-1263 of the nucleotide sequence set forth in SEQ. ID. NO: 18. The sequences are not identical, however, as noted, for example, with respect to the codons beginning at positions 1240, 1222, 1205, and 1129. As described in the specification, SEQ. ID. NO: 18 represents a previously undisclosed sequence encoding an unreported α_1 subunit of a calcium ion channel; thus a protein

comprising the amino acid sequence encoded by SEQ. ID. NO: 19 also represents such an α_1 subunit, which subunit is not identical, but is similar, to that of SEQ. ID. NO: 18.

As set forth in the specification, on page 15, line 2, using the disclosed sequences and conditions of medium hybridization stringency, additional α_1 subunit encoding sequences can be recovered. Medium stringency conditions are those typically used in retrieving similar nucleotide sequences which represent alternative forms such as allelic variants and corresponding coding sequences in different species. These conditions would not retrieve the known $\alpha_{1A, 1B}$, etc. subunits but are sufficient to capture clones encoding the new class of α_1 subunits disclosed herein. By virtue of the discovery of these novel α_1 subunits, it is now possible to screen for substances which are antagonists or agonists of these important calcium ion channels, and to assess the activity of these channels in conjunction with a known range of deleterious conditions as set forth in the specification (p. 9, ll. 1-6). It is also possible to determine the tissue distribution of these channels (p. 16, ll. 14-19. Absent the ability to construct and manipulate these calcium channels, elucidation of the physiological and molecular basis for these conditions would not be possible, and the design of protocols to treat them would be based on trial and error rather than on rational design.

Formal Matters and Sequence Listing

Applicants note the requirement for supplying SEQ. ID. Numbers to Figures 1A and 1B. An addendum to the sequence listing providing such SEQ. ID. Numbers is forthcoming.

Also, as a formal matter, a review of SEQ. ID. NOs: 18 and 19 as filed verifies that these SEQ. ID. NO. presentations contain both a nucleotide sequence and a deduced amino acid sequence. It appears that a putatively corrected sequence listing was submitted on 26 October 1999 in response to a criticism of the previously submitted listing, apparently because of defects to the presentation relating to lack of assignment of numbers to amino acids and an excessive number of characters per line. The present applicants will resubmit a sequence listing complying with the appropriate rules, which contains the corrections *and* includes deduced amino acid sequences as SEQ. ID. NOs: 18 and 19.

Rejections Under 35 U.S.C. § 112, second paragraph

The Office has objected to certain terms in the previously pending claims, such as "non-stringent conditions", "neuronal calcium channel", "sequences of nucleotides that hybridize", and "α_{-11} subunit". These terms no longer appear in the claims. However, the claims as amended refer to "conditions of medium hybridization stringency." This stringency is understood by those in the art to be adequate to retrieve closely related sequences, such as allelic variants, etc., as described above. However, the stringency is such that sequences encoding members of different families of ion channels, for example, would not hybridize. This claim language is supported on page 15 of the specification, line 2. The definiteness of this term is verified by the enclosed Declaration of Dr. Terry P. Snutch, an inventor herein and an expert in this field. As to the objection regarding amino acid sequences putatively included in SEQ. ID. NO: 18 and SEQ. ID. NO: 19, this objection has been addressed above. It is believed helpful to the reader to have the deduced amino acid sequences displayed in the sequence listing and the resubmission will accomplish this. In the meantime, reference may be made to the sequence listing filed with the application.

Accordingly, the rejections under 35 U.S.C. § 112, paragraph 2, may be withdrawn.

Rejection Under 35 U.S.C. § 101 and § 112, first paragraph

The rejection for asserted lack of utility in paragraphs 7 and 8 of the Office action is respectfully traversed. Applicants appreciate the recognition that specific utilities are disclosed in the application, and dispute the position taken by the Office that these utilities are not substantial. The Office cites *Brenner v. Manson* in support of its position, but a comparison of the facts herein and the facts in *Brenner v. Manson* should be convincing that this case is not controlling.

Manson's claims were directed to a process to make a novel steroid that had no disclosed biological function, except that it might be effective in some metabolic sense. The Supreme Court held that because the only utility disclosed for this compound is to find out what it does (and it might do nothing) the process for preparing it could not be considered useful in compliance with the statute.

Here, on the other hand, the claims are directed to a nucleotide sequence which encodes a calcium ion channel which, because it occurs in humans and is functional in a manner that is

associated with various conditions set forth in the specification, such as epilepsy, migraine, ataxia, and cardiac disease, is useful *per se*. It is known from well established studies on the analogous N and L channels that these ion channels are affected in these conditions. Because the channels of the invention are part of the physiological makeup of humans, it is a foregone conclusion that malfunctioning of these channels will be deleterious. The only way it will ever be possible to fine-tune the treatment of defects in these channels as they are associated with any particular disease, i.e. those conditions set forth above, is to use the tools supplied by the invention to make the correlation and thus to provide a means for screening agonists or antagonists which could be used in treatment.

This is in contrast to the situation in *Brenner v. Manson* where the steroid in question is irrelevant metabolically. There is no need to find out whether the steroid behaves in one way or another, it has no function in the normal physiology of the organism. The α subunit of the present invention, on the other hand, is an integral part of this functioning and absent its identification and placing it in the hands of those skilled in the art, it will never be possible to map the sequelae which are associated with abnormalities associated with calcium channel deficiencies or hyperactivity.

Thus, there is a fundamental difference between the demands for usefulness of an arbitrarily chosen compound which is irrelevant to the natural functioning of the organism and a compound which is essential for normal physiology. The latter compound is intrinsically and inherently useful. Without its identification, characterization, and preparation, the physiological basis for abnormal conditions cannot be understood and therefore cannot be effectively treated.

Accordingly, the rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, based on an asserted lack of utility may be withdrawn.

With respect to the objections raised in paragraph 9, applicants are unclear as to the precise nature of the rejection. However, it is inaccurate to state that the specification contains no disclosure of an actual molecule isolated by the applicants. Attention is called to page 14, lines 12-21, which describe the isolation of the 567 nucleotide PCR product represented by SEQ. ID. NO: 19 which was amplified from a human brain total RNA preparation. Thus, the molecule represented by the nucleotide sequence in SEQ. ID. NO: 19 was indeed isolated. The amino acid sequence was simply deduced from the isolated nucleotide sequence. Applicants have explained their basis for concluding that the nucleotide sequence of SEQ. ID. NO: 19 indeed encodes a

portion of a novel human α_1 subunit. It retains sufficient characteristics of α_1 subunits to verify that it is a member of this group, but is sufficiently different from the known members of this family to distinguish it.

With respect to the DNA molecule having a nucleotide sequence as set forth in SEQ. ID. NO: 18, although the nucleotide sequence which contains this sequence is provided in a deposited bacterial artificial chromosome, SEQ. ID. NO: 18 is itself novel and inventive, since it does not include the introns contained in the deposited sequence and is adjusted to proper reading frame.

Accordingly, the objections set forth in the second paragraph, under No. 9 in the Office action may be withdrawn.

The second portion of the rejection in paragraph 9 refers to hybridization conditions and is moot.

Rejection Under 35 U.S.C. § 112, first paragraph

The rejections in paragraph 10 seem similar to those set forth in paragraph 9 and again applicants are unsure as to exactly what the basis for rejection is. It appears that the Office has concluded that the claims are directed to full-length genes as defined by their occurrence in the genome. Respectfully, neither the previously proposed claims, nor the claims as amended require disclosure of the entire native gene. A reading of the claims will verify that all that is required is a DNA molecule which comprises the nucleotide sequence actually set forth in SEQ. ID. NO: 18 or SEQ. ID. NO: 19 (or sequences closely related thereto) and nothing more. Applicants believe that these claims are consistent with the currently existing guidelines on written description. Applicants have completely described the required nucleotide sequence and have taught, for example, in Example 2, how to include such a sequence in expression vectors. Furthermore, once the nucleotide sequence has been disclosed, one of ordinary skill could readily construct expression vectors and host cells containing them. The subject matter was described in the application as filed both in the claims and in the specification. Accordingly, this basis for rejection may also be withdrawn.

CONCLUSION

Applicants have claimed two nucleotide sequences encoding at least a portion of a newly discovered α_1 subunits which can function as calcium ion channels. There is no art rejection of record. As amended, the claims are directed to DNA molecules comprising these nucleotide sequences which are fully disclosed. As explained above, these DNA molecules are inherently useful, unlike the compound that was the subject of *Brenner v. Manson*. Accordingly, it is believed that the presently pending claims, claims 16-33 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 381092000700. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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